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Review

Photodynamic therapy and diagnosis: Principles and comparative aspects

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ABSTRACT

Photodynamic therapy (PDT) is an evolving method of treating superficial tumours that is non-invasive and carries minimal risk of toxicity. It combines tumour-selective photosensitiser dyes, tissue oxygen and targeted illumination to generate cytotoxic reactive oxygen species (ROS) within the tumour. In addition to directly acting on tumour cells, PDT damages and restricts tumour microvasculature, and causes a local inflammatory response that stimulates an immune response against the tumour. Unlike surgery or radiotherapy, the surrounding extracellular matrix is unaffected by PDT; thus, tissue healing is excellent and PDT seldom causes scars. This, combined with the ease of light application, has made PDT a popular treatment for cancers and pre-cancerous conditions in human beings. Moreover, because photosensitiser dyes are fluorescent and selectively accumulate in tumour tissues, they can additionally be used to visualise and discriminate tumour from normal tissues, thereby improving the accuracy of tumour surgery. In veterinary practice, PDT has been used successfully for treatment of superficial squamous cell carcinomas of the feline nasal planum; urinary tract, urinary bladder and prostate neoplasia in dogs; and equine sarcoids. The purpose of this article is to provide a comparative review of the current literature on PDT in human and veterinary medicine, and to establish a basis for future development of PDT in veterinary medicine.

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Introduction

Photodynamic therapy (PDT) involves administration of a photosensitiser drug, or a pro-drug, which selectively accumulates in target cells, followed by local illumination of the lesion with visible light (Lukšiene, 2003; Wachowska et al., 2011). It is a minimally invasive therapeutic technique used in the management of various cancerous and pre-malignant diseases. The photosensitiser can also be visualised in tumour cells using an appropriate set of imaging filters to provide a means of tumour detection (Hefti et al., 2010; Mowatt et al., 2011; Nguyen and Tsien 2013; Allison 2016).

In addition to cancer treatment, PDT has been used for the treatment of microbial infections in human beings (Kharkwal et al., 2011; Sharma et al., 2012; Wardlaw et al., 2012), dogs (Fabris et al., 2014) and sheep (Sellera et al., 2016). PDT has also been used for light-triggered uptake of pharmaceutical agents that otherwise

would become entrapped and destroyed within cellular endosomes (photochemical internalisation, PCI; Selbo et al., 2015; Madsen, 2016).

The origins of PDT can be traced back to ancient Egypt, where photosensitising plant pigment extracts were applied to the skin and exposed to sunlight as a treatment for psoriasis (Daniell and Hill, 1991). The use of PDT for treatment of various human skin cancers was first investigated in the 1970s by Dougherty et al. (1978). Thomas Dougherty's use of a haematoporphyrin derivative was based on the pioneering work of Policard (1924), who demonstrated that porphyrins were preferentially distributed into malignant rather than normal tissues. The technique was slow to gain acceptance because the 'first generation' photodynamic agents were slow to clear from normal cells, with the result that treated human patients had to remain out of bright light (e.g., sunlight) for several weeks to avoid severe skin reactions. However, the potential for the technique in treating locally advanced carcinomas of the head and neck (Wile et al., 1984), urinary bladder (Misaki et al., 1983), oesophagus and bronchus (Cortese and Kinsey, 1984) outweighed this caveat and stimulated further research.

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The availability of haematoporphyrin derivatives with faster tissue clearance times stimulated more interest in PDT and numerous human clinical trials have now been published, showing encouraging results with photosensitising dyes administered topically or systemically (orally or intravenously) or instilled into hollow organs (e.g. urinary bladder). A limited number of veterinary studies have been published, also showing promise. A previous review of PDT in veterinary medicine was published by Buchholz and Walt (2013); since then, further advances have been made. The purpose of this review is to describe the basic principles of PDT and discuss the clinical application of PDT in human beings and animals for cancer treatment and diagnosis.

Fundamentals and mechanisms

There are three basic requirements for PDT: (1) a compound with photosensitising properties (photosensitiser, PS); (2) a source of visible light; and (3) oxygen. The photosensitiser is a chemical/dye that selectively accumulates in malignant tissues and can be activated by visible light. Energy from the light-excited PS is transferred to oxygen molecules (O_2) to give reactive oxygen species (ROS), notably singlet oxygen (1O_2) and superoxides, which damage biological molecules, initiating a cascade of biochemical events, culminating in damage and death of neoplastic cells (Fig. 1) (Dougherty et al., 1998; Juzeniene et al., 2007). Increasing tissue oxygenation can lead to increased ROS formation during PDT and improved outcomes (Maier et al., 2000).

The mechanisms by which different photosensitisers localise selectively in malignant tissues are complex and not fully understood. Physical factors, such as increased vascular permeability and poor lymphatic drainage in tumours, coupled with an affinity for proliferating endothelium, are likely to contribute to their accumulation in tumours (Dougherty et al., 1998).

Three main processes by which ROS contribute to the destruction of tumours by PDT are direct cellular damage, indirect vascular shutdown and activation of immune responses against tumour cells (Dougherty et al., 1998; Dolmans et al., 2003; Solban et al., 2006). Direct damage to tumour cells can result in cell death by both programmed pathways (apoptosis) and non-programmed pathways (necrosis) (Oleinick et al., 2002; Igney and Krammer, 2002; Allison and Moghissi, 2013a). Generally, when the light intensity is low, apoptotic cell death may be initiated (Agarwal et al., 1991; Allison and Moghissi, 2013b). At higher light intensities, tumour cells are rapidly ablated by necrosis due to destruction of cellular and subcellular membranes. This also leads to release of cytokines and lysosomal enzymes (Henderson and Fingar, 1987), causing damage to cells nearby, the so-called bystander effect (Dahle et al., 1997; Allison and Moghissi, 2013a). Release of inflammatory mediators from the treated region stimulates activation of leucocytes, including neutrophils and macrophages, and significant tumour cell death occurs through these activated immune cells (Coutier et al., 1999; Gollnick et al., 2003; Castano et al., 2006). This observation has led to the development of combination therapies of PDT with

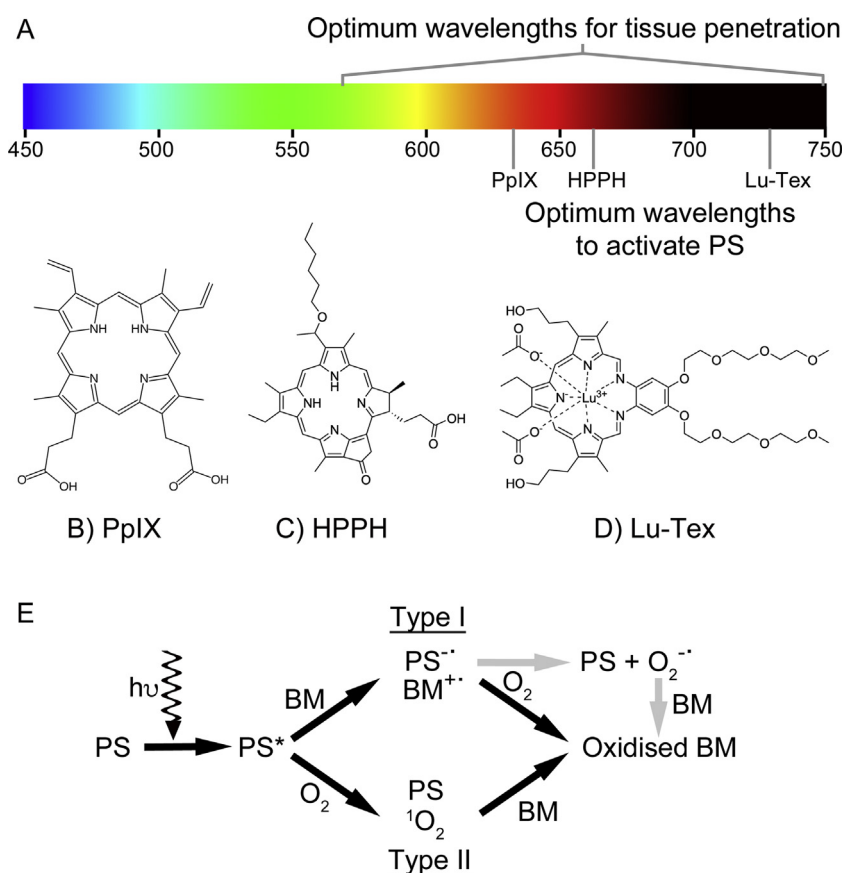


Fig. 1. Fundamentals of photodynamic therapy. (A) Visible and near infra-red light spectrum showing the wavelengths (nm) of maximum tissue penetration by light (above) and absorbance maxima of selected photosensitisers (below). (B–D) Chemical structures of selected photosensitisers. (E) Mechanism of action of photosensitising agents. The photosensitiser (PS) becomes activated (PS^*) by light ($h\nu$). PS^* can undergo two types of reaction. In type I reactions, biological material (BM) interacts directly with PS^* forming ion radicals of both species ($PS^{\bullet+}$ and $BM^{\bullet-}$). The BM radical interacts with oxygen and becomes oxidised. The PS radical is either destroyed or reacts with oxygen to regenerate PS and make a superoxide anion ($O_2^{\bullet-}$) that can react with BM to oxidise it. In type II reactions, PS^* interacts with oxygen to regenerate PS and make singlet oxygen (1O_2), which reacts with BM to oxidise it.

immunotherapy, by including immunoadjuvants against tumour-specific epitopes (Qiang et al., 2008; Kleinovink et al., 2015).

PDT also mediates a vascular effect within tumours (McMahon et al., 1994; Abels, 2004). Neovascular tumour endothelial cells may accumulate higher levels of PS than normal endothelium (Debeve et al., 2011) and, following PDT, microvascular collapse can be observed and can lead to severe and persistent post-PDT tumour hypoxia (Star et al., 1986; Henderson and Fingar, 1987; Chen et al., 2003). PDT may also lead to vessel constriction via inhibition of the production or release of nitric oxide by the endothelium (Gilissen et al., 1993).

An important clinical consideration is effective analgesia. In human beings, PDT produces a sensation of stinging or burning during illumination, especially in sensitive areas, such the face and scalp (Halldin et al., 2011; Chaves et al., 2012). Treatment of large skin areas generally produces more pain than smaller areas (Grapenglosser et al., 2002; Halldin et al., 2011; Chaves et al., 2012).

Photosensitisers for photodynamic therapy

Photosensitising agents are natural or synthetic chemicals that transfer light energy to neighbouring molecules, importantly to dissolved oxygen (Allison et al., 2004). Most of the photosensitisers used in cancer therapy are based on a tetrapyrrole structure, similar to that of the protoporphyrin contained in haemoglobin. In clinical practice, a successful PS agent is: (1) nontoxic until light activated; (2) hydrophilic for easy systemic application; (3) activated by a clinically useful light wavelength; and (4) reliably generates a photodynamic reaction (PDR). Ideally, it also concentrates in tumours, clears normal tissue quickly and is eliminated from the patient relatively rapidly (Allison and Moghissi, 2013a).

The first-generation photosensitiser haematoporphyrin derivative (HPD) was a mixture of various monomers, dimers, and polymers of haematoporphyrin (Allison and Moghissi, 2013a). The commercially available product, porfimer sodium, marketed under the tradename Photofrin, was used experimentally in healthy dogs (Tochner et al., 1991; Panjehpour et al., 1993) and in a canine glioma model (Whelan et al., 1993). It was approved for treatment of early stage human lung cancer in 1998 and for Barrett's oesophagus in 2003. The clinical application of Photofrin has been limited by two factors. First, its absorption peak occurs at 630 nm, which is too short a wavelength to allow deep penetration of light in tissue. Secondly, Photofrin results in cutaneous photosensitivity lasting up to six weeks (Zhu and Finlay, 2008).

These limitations stimulated the development of a second generation of photosensitisers with improved efficiency of ROS generation, more rapid clearance, fewer side effects, and absorption peaks at longer wavelengths (>630 nm red light), where the tissue penetration of light is deeper. One such second-generation photosensitiser is 5-aminolaevulinic acid (ALA), a naturally occurring pro-photosensitiser and precursor for the biosynthesis of the haem molecule. For therapeutic purposes, ALA is administered topically (Morton et al., 2008, 2013), orally (Muller and Wilson, 2006), or intralesionally (Hage et al., 2007; Kim et al., 2012). ALA enters into all cells, but uptake is potentiated by transporters of β amino acids and γ -aminobutyric acid (GABA) (Rud et al., 2000), which are highly expressed on some cancer cells and neurones, respectively (Zhang et al., 2013). It is then metabolised to the red-fluorescent photosensitiser protoporphyrin IX (PpIX, absorption at 635 nm) and finally to non-fluorescent haem (Ajioka et al., 2006; Allison and Moghissi, 2013a). This final step relies on ferrochelatase to add ferrous iron (Fe^{2+}) to PpIX; this rate-limiting enzyme is often deficient in cancer cells (Kemmner et al., 2008). Thus, in the presence of excess ALA, cancer cells that combine high ALA uptake with low PpIX destruction will accumulate PpIX photosensitiser (Collaud et al., 2004). Clinical

advantages of ALA treatment include rapid clearance of PpIX from the tissue within 12 h, resulting in short-lived cutaneous photosensitivity. In human patients, ALA has been used for the treatment of cutaneous T cell lymphoma (Coors and von den Driesch, 2004), basal cell carcinoma (Kim et al., 2012), squamous cell carcinoma (SCC) and other head and neck cancers (Grant et al., 1993; Morton et al., 1996). In veterinary medicine, ALA has been used to treat SCC in a cow (Hage et al., 2007) and in cats (Bexfield et al., 2008), sarcoids in horses (Gustafson et al., 2004; Golding et al., 2017) and transitional cell carcinoma (TCC) in dogs (Lucroy et al., 2003a,b) (Tables 1 and 2).

The hydrophilic nature of ALA limits its ability to penetrate intact skin deeply and thereby restricts the use of topically applied ALA-PDT to the treatment of superficial diseases where the tissue structure is disorganised. To overcome this limitation, ALA esters, which are less hydrophilic than the parental compound, have been developed. The methyl ester of ALA, methyl-aminolaevulinate (MAL, Metvix, or Metvixia), was approved by the US Food and Drug Administration (FDA) for PDT treatment of actinic keratosis in 2004 and has shown good results in treatment of equine sarcoids (Kemp-Symonds, 2012; Golding et al., 2017). Hexaminolaevulinate, the *n*-hexyl ester of ALA (HAL, Hexvix, Cysview), which is converted to PpIX 50–100 times more efficiently than ALA, was licensed in the US in 2010 for the detection of human urinary bladder cancer (Furre et al., 2005). Hexaminolaevulinate has also been used intra-operatively in a PDT model in dogs with prostate carcinoma (L'Eplattenier et al., 2008).

Several other second-generation photosensitisers have been developed, or are in the process of being developed, each with slightly different origins and characteristics. These include *m*-tetrahydroxyphenyl chlorine (*m*-THPC, Foscan), 2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide-*a* (HPPH, Photoclor), palladium bacteriopheophorbide (Padoporfin, TOOKAD) and its more water-soluble monolysotaurine derivative (Padeliporfin, TOOKAD-Soluble), motexafin lutetium (Lu-TeX, Lutrin); and Verteporfin (Visudyne). The advantages and indications for these newer agents are summarised in Table 1.

Photosensitisers for tumour diagnosis

Photodynamic diagnosis (PDD) uses the fluorescence of photosensitisers to identify tumour tissue *in situ*. PDD fits within the broader category of fluorescence guided surgery (Allison, 2016), the distinction being that, by increasing the illumination intensity or duration, PDD can become PDT. However, whilst the generation of singlet oxygen by photosensitisers is essential for PDT, these same reactive species can damage the photosensitiser and render it non-fluorescent.

ALA has been trialled for PDD in 11 different human tumour types (Nokes et al., 2013) and is licensed in human beings for intraoperative margin assessment in gliomas (Hefti et al., 2010; Stummer et al., 2006) and the *n*-hexyl derivative for urinary bladder cancer (Kausch et al., 2010; Mowatt et al., 2011). Each of the major surgical microscopy and endoscopy manufacturers (Leica, Olympus, Storz, and Zeiss) have specialised imaging equipment for intraoperative PDD for human surgery. Research versions are available for animal models (e.g. Solaris system, Perkin Elmer). However, relatively little work has been done on translating human PDD to veterinary surgery. Veterinary examples include intraoperative cancer imaging and staging in dogs (Knapp et al., 2007; Cabon et al., 2016; Osaki et al., 2016), and image-guided surgery in cats (Wenk et al., 2013). The next generation of agents for photodiagnosis are generally based on near infra-red dyes, which allow deeper views into tissues, sometimes complexed with tumour-targeting peptides or antibodies (Luo et al., 2011; Wenk et al., 2013).

Table 1

Summary of characteristics and application of selected second generation photosensitisers to treat tumours.

Agent (synonyms), manufacturer	Activation wavelength (nm)	Advantages	Applications ^a	References
Foscan (m-tetrahydroxyphenyl chlorine (mTHPC), temoporfin), Biolitec Pharma	525–660	Short duration of skin photosensitivity (15 days) High quantum yield for singlet oxygen Depth of tumour necrosis (10 mm)	Pleural mesothelioma Head and neck cancers Oesophageal cancer Prostatic cancer Pancreatic cancer Skin tumours Skin tumours (cats)	Friedberg et al. (2003) Biel (2006) Etienne et al. (2004); Lovat et al. (2005) Nathan et al. (2002); Moore et al. (2006) Pereira et al. (2007) Triesscheijn et al. (2006) Buchholz et al. (2007)
Photochlor (2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide (HPPH)), AdooQ Bioscience	665–680	Extremely hydrophobic, increasing penetration into tissue	Obstructive oesophageal cancer Oral SCC (dogs) Facial SCC (cats) SCC (horses)	Dougherty et al. (2000) McCaw et al. (2000) Magne et al. (1997) Giuliano et al. (2008)
TOOKAD (WST-09, Padoporfin, palladium bacteriopheophorbide), Steba Biotech	760	New generation photosensitiser with greater stability and short half-life	Prostatic carcinoma (dogs)	Huang et al. (2005); Nomura and Mimata (2012)
Padeliporfin (TOOKAD Soluble, WST-11, palladium bacteriopheophorbide monolysotaurine), Steba Biotech	760	Vascular-targeted PDT	Prostatic carcinoma Prostatic carcinoma (dogs)	Azzouzi et al. (2017) Chevalier et al. (2013)
Lu-Tex (Motexafin lutetium, lutetium texaphyrin, Pharmacyclics)	730	Water soluble. Selectively retained in tumour Only 24–48 h skin photosensitivity	Prostatic carcinoma Rectal (dogs)	Patel et al. (2008) Ross et al. (2006)
Talaporfin sodium (aspartyl chlorin, Laserphyrin, Aptocine), Meiji Seika Pharma	664–667	Retained in tumour for 50 h	Lung tumours Oesophageal tumours Intranasal tumours (dogs)	Usuda et al. (2007) Yano et al. (2017) Ishigaki et al. (2017)
5-Aminolaevulinic acid (ALA), various manufacturers	414, 635	Short loading (3 h)	ALA: At least 11 different human tumours	Nokes et al. (2013)
	All pro-drugs (metabolised to protoporphyrin IX)	Short skin photosensitivity (12 h)	ALA: Equine sarcoids	Golding et al. (2017)
Methyl-ALA (MAL, Metvix), Galderma		Epithelial penetration improves in sequence: ALA > MAL > HAL	MAL: Basal cell carcinoma MAL: Equine sarcoids	Morton et al. (2008, 2013) Kemp-Symonds (2012); Golding et al. (2017)
Hexyl-ALA (HAL Hexvix), Ipsen			HAL: Prostate tumours (photodynamic detection) Prostatic carcinoma (dogs)	Furre et al. (2005) L'Eplattenier et al. (2008)
Verteporfin (Visudyne), Novartis	689–693	Binds low density lipoprotein receptors on abnormal blood vessels and tumours	Wet macular degeneration Oesophagus (dogs) SCC (horses)	Scott and Goa (2000) Panjehpour et al. (2002) Giuliano et al. (2014)

SCC, squamous cell carcinoma.

^a Applications are for human beings unless stated.

Light sources and delivery systems

The primary requirement when treating lesions with PDT is to ensure that sufficient, homogenous light is delivered to the target tissue. Each PS has an optimal wavelength and intensity (fluence) of light for activation (Sibata et al., 2001). Choice of light source should therefore be based on PS absorption (fluorescence excitation and action spectra), location, size and accessibility of lesions, and tissue characteristics. The clinical efficacy of PDT is dependent on complex dosimetry, comprising total light dose, light

exposure time and light delivery mode (single versus fractionated or even metronomic). The fluence rate also affects PDT response (Henderson et al., 2006), as demonstrated in tumour bearing cats by Hahn et al. (1998).

The wavelength of light used for PDT is typically in the range of 600–800 nm, the ‘therapeutic window’ (Wilson and Patterson, 1990). In this wavelength range, the energy of each photon (1.5 eV) is sufficient to excite the photosensitiser and yet is low enough to allow the light to penetrate up to 2 cm into the tissue (Zhu and Finlay, 2008).

Table 2

Overview of clinical reports of photodynamic therapy (PDT) for superficial squamous cell carcinoma (SCC) and SCC in situ in cats.

Cases/tumour location	PDT agent	PDT method	Response rate/outcome/side effects	References
51 cats Cutaneous SCC facial skin	Pyropheophorbid- α -hexyl-ether (HPPH-23)	IV administration Argon-pumped dye laser	Overall 61% response rate at 1 year 100% T1a tumours, 56% T1b and 18% T2b No toxicity, but some morbidity	Magne et al. (1997)
4 dogs and 4 cats Superficial carcinoma	HPPH	IV administration LED (100 J/cm ² , 33 min)	8/9 CR >50% PFS > 68 weeks No cutaneous photosensitivity	Reeds et al. (2004)
13 lesions/cats 10 nasal planum 2 pinna 1 eyelid	5-Aminolaevulinic acid (ALA), cream	Topical application LED 635 nm 12 J/cm ²	85% CR rate but with 64% local recurrence (median 21 weeks) Cats attempt to scratch lesion after treatment Local analgesia required	Stell et al. (2001)
18 cats 20 cutaneous SCC	Liposomal formulation of Foscan (m-THPC)	IV administration 625 nm diode laser	100% CR rate Overall 1-year control rate 75%, 20% recurrence (172 days) Mild erythema/oedema in 15% of cats	Buchholz et al. (2007)
55 cats Superficial SCC nasal planum	ALA, cream	Topical application LED 635 nm 12 J/cm ²	85% CR rate, 11% PR rate, but with 51% recurrence (median 157 days) Transient, mild, local adverse effects	Bexfield et al. (2008)
12 cats Cutaneous SCC (7 pinna, 2 nasal planum)	Haematoporphyrin derivative (Photogem)	IV administration LEDs (300 J/cm ² , 30 min)	No response in invasive tumours or pinna Small non-infiltrative lesions of nasal planum ($n=3$) showed CR/PR One cat developed nasal oedema and died	Ferreira et al. (2009)

LED, light-emitting diode; CR, complete response; PFS, progression-free survival; PR, partial response.

The development of light sources and delivery devices with the appropriate dosimetric parameters are key components for the clinical application of PDT. Accurate delivery of the light to the tumour tissue can be accomplished by a variety of light sources and fibre optic delivery devices. Lasers have been one of the main light sources used in PDT. Modern diode lasers are portable and do not require specialised electrical supply or water cooling, providing excellent stability of output power over long periods of time (Mang, 2004). Diode lasers have been approved for use in human oesophageal and lung cancer at 630 nm (Photofrin) and at 652 nm (Foscan) (Yoon et al., 2013).

Alternatives to laser technology are non-coherent light sources (Reeds et al., 2004) and light emitting diodes (LEDs), the latter where light is produced by electroluminescence. LEDs are compact, lightweight and require significantly less energy than lasers. LED systems are capable of output powers up to 150 mW/cm² over a 3 cm × 3 cm area. LEDs have been manufactured with various light output wavelengths, such as 630, 670 and 690 nm, which can be used in PDT procedures for flat surface illumination (Mang, 2004, 2009). Light delivery for treatment of large surface areas, such as treatment of skin diseases, may also be accomplished using broad spectrum fluorescent lamps (Marcus and McIntyre, 2002). However, LEDs have been shown to be more effective than fluorescent lamps for PDT treatment of SCC (Novak et al., 2016). One obvious source of light for PDT is the sun; several recent studies have demonstrated the effectiveness of daylight PDT (See et al., 2016). Daylight PDT has obvious potential for veterinary skin cancers, provided the tumour is located where it will be in constant daylight.

In addition to the light source, delivery devices may be required to provide penetration of light into the target tissue (Star et al., 1992). Fibre-optic devices have been developed for PDT light delivery and dosimetry (Sternborg et al., 2013). The most widely used fibre-optic device in PDT is a cylindrical diffusing fibre tip available in lengths of 1–9 cm depending on the specific application. Two light delivery methods have been developed: intraluminal irradiation using light diffusers for the lung and oesophagus, and interstitial illumination methods to deliver

adequate light doses to the target tumour volume in head and neck cancers (Yoon et al., 2013). Fibre optic delivery of PDT has been used in dogs to treat intramedullary bone tumours (Burch et al., 2009).

Photodynamic therapy and diagnosis: Clinical uses in human beings and animals

In contrast to its increasing use in human medicine, the use of PDT in veterinary medicine has been relatively limited. Although results from small veterinary clinical studies have been published, and even though the dog and cat have been used as preclinical models in several studies (Lucroy et al., 1999, 2003b; Griffin et al., 2001; Panjehpour et al., 2002; Tanabe et al., 2004), PDT is not well established as a treatment option for tumour bearing animals to date. The main indication currently is in treatment of in situ carcinoma/SCC in cats. Other possible indications are urinary tract neoplasia and gliomas in dogs, and SCC and sarcoids in horses (Buchholz and Walt, 2013). The following is a comparative review of the clinical experience of application of PDT in human and veterinary medicine. This should provide a basis for future developments and applications of PDT in veterinary medicine.

Cutaneous tumours

Carcinoma in situ/squamous cell carcinoma

ALA-PDT is mainly used to treat dermatological cancers in human beings (Morton et al., 2008, 2013; Wan and Lin, 2014). The results of ALA-PDT in the treatment of human Bowen's disease (SCC in situ) have been promising; randomised, controlled trials comparing ALA-PDT or MAL-PDT to cryotherapy or 5-fluorouracil (5-FU) cream revealed complete response rates of 82–100% for PDT, 67–100% for cryotherapy and 79–94% for 5-FU at 12–24 months (Morton et al., 1996; Salim et al., 2003). The efficacy of topical ALA-PDT in the management of primary cutaneous invasive SCC is variable, with response rates of 54–100% reported for superficial lesions and recurrence rates of

0–69%, but with reduced efficacy in more nodular lesions (Wolf et al., 1993; Morton et al., 2002). Current evidence supports the potential of topical ALA-PDT for superficial, micro-invasive SCC; however, topical PDT cannot be recommended for invasive SCC in view of the metastatic potential of these tumours (Morton et al., 2008, 2013).

Cutaneous in situ carcinoma/SCC in the cat represents the main application for PDT in veterinary medicine to date (Fig. 2). A number of studies have reported response rates from 60% to >80%, and disease-free intervals >68 weeks, for topical and systemic PDT in cats using a variety of photosensitisers (Table 2). As is the case in human patients, the smaller and less invasive tumours respond best to PDT (Magne et al., 1997). PDT has also been used to treat SCC in dogs (McCaw et al., 2000), horses (Giuliano et al., 2008), a cow (Hage et al., 2007), snakes (Roberts et al., 1991) and a great hornbill (*Buceros bicornis*) (Suedmeyer et al., 2001).

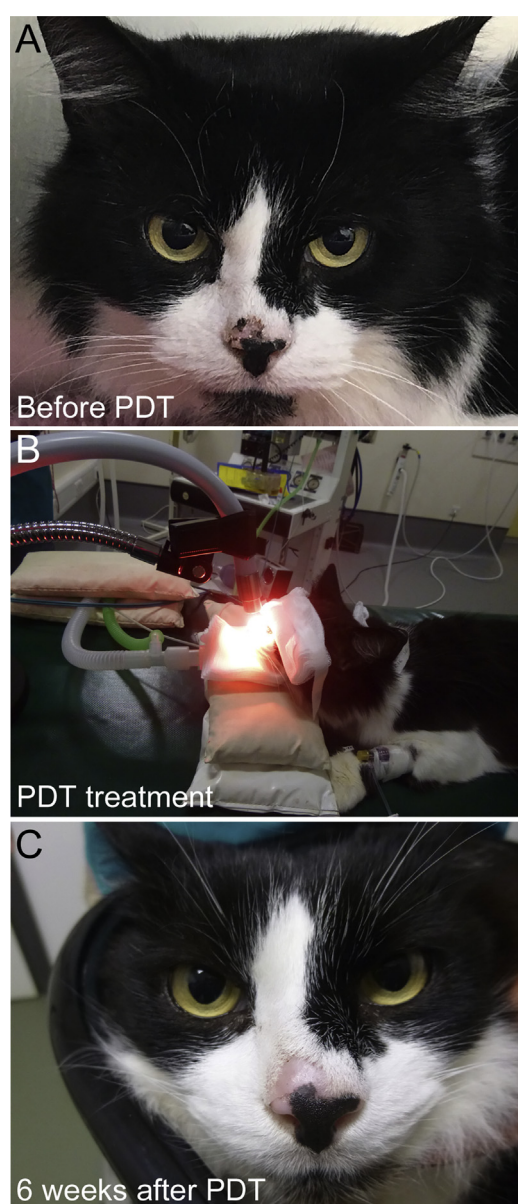


Fig. 2. Feline nasal squamous cell carcinoma (SCC). (A) An early SCC on the right nasal planum in a domestic short-haired cat. (B) Application of photodynamic therapy (PDT) using a high intensity light-emitting diode (LED). (C) Complete resolution of the lesion at 6 weeks, with minimal scar formation.

Basal cell carcinoma

PDT has been employed successfully for treatment of basal cell carcinoma (BCC) in human patients as a sole agent or in neoadjuvant setting (Berroeta et al., 2007; Rhodes et al., 2007). A 92% complete response rate was reported with topical ALA-PDT in 330 human patients with superficial BCC, but the response rate dropped to 71% in patients with nodular BCC (Zeitouni et al., 2001). When topical PDT (with ALA or MAL) was compared to surgery for BCC, PDT consistently showed an increased recurrence rate for both superficial and nodular BCC (Basset-Seguín et al., 2008). This may be due to insufficient penetration of the photosensitiser to deeply located tumour cells when the PS is applied topically. To overcome this problem, the PS may be injected intralesionally. Twenty human patients with nodular BCC were treated with ALA in 1% saline solution at estimated dose of 1 mL/cm² injected into the base of tumour. PDT resulted in tumour necrosis, followed by complete re-epithelisation after 4–6 weeks, with good cosmetic results, no histological evidence of BCC after 3 months and no recurrence during follow-up of 19.5 months (Rodríguez-Prieto et al., 2012).

Experience of intralesional injection of PS is limited in veterinary species. One study reported PDT in a cow with ocular SCC using intratumoural injection of ALA. A complete response was observed after 3 months and no relapse at 12 months after the treatment (Hage et al., 2007). A pilot study was conducted using surgical resection plus PDT for periocular SCC in horses by infiltrating wound beds with HPPH prior to illumination (Giuliano et al., 2008); this combination yielded disease-free intervals of 25–68 months. The overall recurrence rate was 2/9 (22%) horses; for those horses where local PDT was the first and only treatment modality used, the recurrence rate was 0%.

Equine sarcoids

Although of fibroblastic rather than of basal cell origin, equine occult and nodular sarcoids form dermal nodules or plaques and, as such, bear some physical resemblance to human nodular BCC. Currently there is no 'gold standard' treatment for equine sarcoids; however, PDT has shown promise in the treatment of these common and frustrating lesions. Several small studies have reported encouraging response rates using topical or locally injected ALA or MAL in equine occult and nodular sarcoids. Gustafson et al. (2004) achieved a 72% treatment response using ALA-PDT, with recurrence of 7/18 (39%) lesions after 2 years. Due to their size, cytoreductive surgery may significantly improve the response for larger lesions. In one study, CO₂ laser excision with adjunctive MAL-PDT achieved 1 year disease-free in 93% of horses (Kemp-Symonds, 2012). A single application of topical ALA-PDT, followed by glycolysis inhibition, resulted in successful treatment of equine sarcoids up to 5 mm thick with a response rate of 25/27 (93%) after 1 month, compared with 1/7 (14%) using ALA-PDT only (Golding et al., 2017) (Fig. 3).

Prostate cancer

In men, definitive management of early stage prostate cancer with either surgery or ionising radiation therapy is associated with significant associated morbidities due to the proximity of nerves, the urinary bladder and the rectum. In contrast, PDT has the potential to selectively treat the prostate gland, while sparing the surrounding normal tissues, because light can be delivered to the entire gland using interstitial cylindrically diffusing optical fibres. Prostate cancer is therefore an attractive target for PDT (Agostinis et al., 2011; Ahmed et al., 2012).

Vascular-targeted PDT using Padeliporfin-mediated PDT and a short drug-to-light interval was shown to carry minimal toxicity in

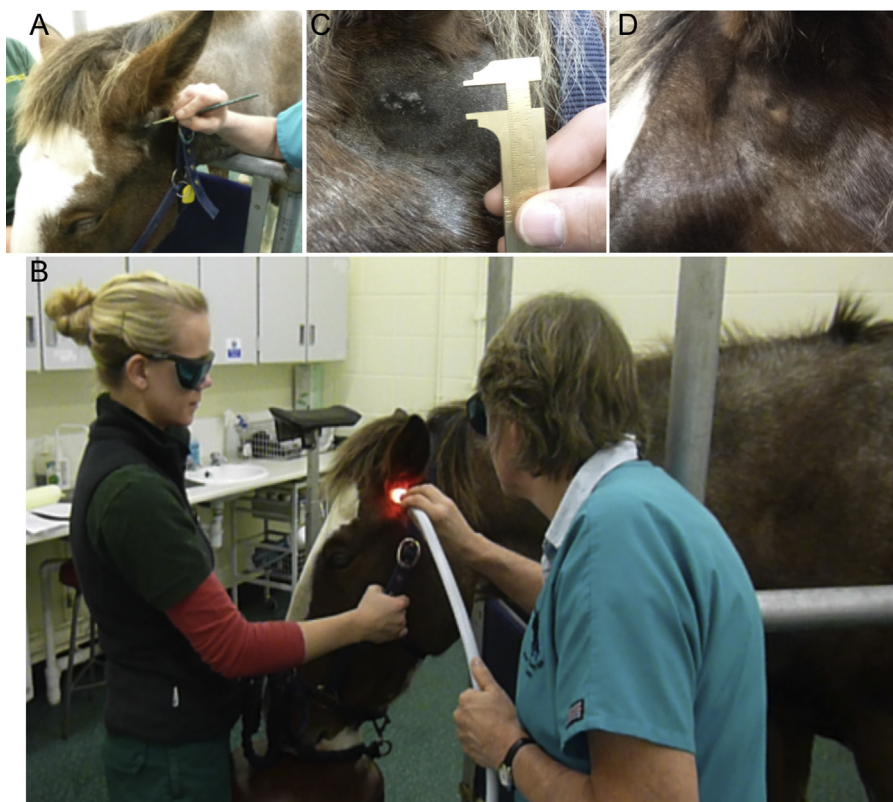


Fig. 3. Treatment of equine sarcoids. (A) Painting 5-aminolaevulinic acid (ALA) onto a sarcoid. (B) Application of photodynamic therapy (PDT). (C) Appearance of sarcoid at time of PDT treatment. (D) Appearance of sarcoid one month after PDT.

a phase I trial of human prostatic carcinoma patients ($n = 24$) with local failure following radiotherapy (Weersink et al., 2005; Trachtenberg et al., 2007). In a follow-up phase II study, patients were treated with increasing light doses. At 6 months, all patients where $>60\%$ of the prostate gland was determined to be avascular by post-PDT magnetic resonance imaging had negative biopsies, however, 2/28 (7%) patients developed urethrorrectal fistulae (Trachtenberg et al., 2008). Following refinement of the technique, a recent phase III randomised controlled study of Padeliporfin vascular-targeted PDT (versus active surveillance) has shown this to be a safe and effective treatment for low-risk localised prostate cancer (Azzouzi et al., 2017).

The normal canine prostate gland has served as a useful preclinical model for evaluating responses to PDT in vivo, since its size and general anatomical structure are similar to those of the human prostate (Waters and Bostwick, 1997). An experimental study was conducted assessing Padeliporfin PDT on canine prostate pre-treated with ionising radiation. All dogs had normal spontaneous urination upon recovery from the procedure, with no signs of incontinence or significant macroscopic haematuria (Huang et al., 2004). Vascular-targeted photodynamic therapy with WST11 (TOOKAD Soluble) has been investigated in a canine model of benign prostatic hyperplasia; in 30 treated dogs, prostatic urethral width increased as early as 6 weeks after treatment, while prostatic volume decreased, reaching 25% by 18–26 weeks, this response lasted up to 1 year (Chevalier et al., 2013); the treatment was well tolerated, with only one dog experiencing urinary retention. Unfortunately, canine prostatic carcinoma usually is not detected until clinical signs are exhibited, at which time the disease is in late stage, often with metastatic disease, so it is unlikely that PDT would be beneficial in such cases.

Urinary bladder cancer

Photodiagnosis is used in management of human urinary bladder cancers (Mowatt et al., 2011) and urinary bladder cancer is also a potential target for PDT. Human urinary bladder cancers are often superficial and multifocal, and can be assessed and debulked endoscopically. Furthermore, the geometry of the urinary bladder allows for homogeneous light delivery via diffusing fibres. In general, early response rates (2–3 months) to PDT have been achieved in 50–80% of human patients and longer-term (1–2 years) responses have been achieved in 20–60% of patients. It should be noted that many of the patients treated in these studies had recurrent disease that developed after standard therapies, such as Bacillus Calmette-Guérin (BCG) (Agostinis et al., 2011). Treatment of superficial urinary bladder cancer with PDT is generally well tolerated, with dysuria, haematuria, and skin photosensitivity being the most common acute side effects. Urinary bladder wall fibrosis/diminished urinary bladder capacity can be a problem in some human patients (Prout et al., 1987; Uchibayashi et al., 1995). Studies of locally applied (intravesical) ALA demonstrate that comparable complete response rates of 52–60% at 2–3 years can be achieved for human patients with treatment-refractory urinary bladder carcinoma in situ without the prolonged skin photosensitivity experienced using systemic Photofrin (Berger et al., 2003; Waidelich et al., 2003). Despite these promising results, PDT for urinary bladder cancer remains largely investigational with limited use (Agostinis et al., 2011).

Canine transitional cell carcinoma (TCC) is most commonly located in the trigone region of the urinary bladder, precluding complete surgical resection; palliative medical management is often the only treatment available (Fulkerson and Knapp, 2015). Photodynamic therapy could represent a promising option for dogs

with TCC. However, canine TCC is often diagnosed at a late stage and is more invasive than human urinary bladder cancers, making comparisons with human studies difficult (Fulkerson and Knapp, 2015). In vitro studies have shown, that ALA-PDT destroys canine TCC cells (Ridgway and Lucroy, 2003). When studied in vivo, 70% of dogs vomited after oral administration of ALA, but this did not appear to have a negative impact on pharmacokinetics, and the active metabolite (PpIX) was shown to accumulate in the urinary bladder mucosa, compared to the muscularis and serosa. Five dogs with TCC of the urinary bladder treated with ALA-PDT and a laser fibre delivery system showed transient improvement of clinical signs with tumour progression-free intervals of 4–34 weeks (Lucroy et al., 2003a,b). The application of PDT for canine TCC clearly warrants further investigation.

Brain tumours (gliomas)

Experimental and clinical studies have demonstrated that PDT can complement current standard therapies (surgical resection, radiation therapy and chemotherapy) in the treatment of brain tumours in human beings (Muller and Wilson, 1995, 1996). PDT may be particularly useful as an adjunct to surgery, since it can non-invasively target tumour cells infiltrating the surrounding brain. Initial trials have provided encouraging results using various formulations of haematoporphyrin derivatives (HPD, Photofrin), ALA and m-THPC, with light sources including lamps, dye lasers and diode lasers (Agostinis et al., 2011). One of the main indications for ALA in management of human glioma is in fluorescence guided surgery (FGS). ALA based FGS has been shown to provide longer survival times than conventional surgery in patients with suspected malignant gliomas ($n=322$; 16.7 versus 11.8 months, respectively) (Stummer et al., 2006).

In a canine glioma model, 0.75 mg/kg Photofrin-II was administered intravenously, followed 24 h later by PDT, delivered using a fibreoptic catheter directly to the tumour via a burr hole in the skull (Whelan et al., 1993). This destroyed the tumour without significant brain-stem injury.

The new classes of PSs, the better understanding of dosimetry and further improvements in technology may significantly change the currently achieved clinical outcome for gliomas and other brain tumours both in human and veterinary patients. Pre-clinical data indicate that protracted light delivery may increase the therapeutic index of PDT in the brain, combined with newer technologies, such as implantable LED-based light delivery systems (Kostron, 2010).

Future perspectives

Photodynamic therapy offers great potential due to its selective targeting of tumour cells and minimal normal tissue toxicity. Several innovative strategies have been used to improve PS penetration into tumour cells, including the use of an electric current to draw PS deeper into the skin (Lopez et al., 2003), intratumoural PS injection (Hage et al., 2007; Rodríguez-Prieto et al., 2012), and pre-treatment with chemical penetration enhancers (Malik et al., 1995; De Rosa et al., 2000; Golding et al., 2017), and liposomal formulations and nano-emulsions (Buchholz et al., 2005, 2007).

The efficacy of PDT may also be improved by overcoming the antioxidant defences of cancer cells. Antioxidant defences that remove excess ROS are upregulated in many cancers (Tracootham et al., 2009), undermining the full potential of PDT. Combination of glycolysis inhibitors with PDT has been shown to deplete cellular antioxidants and significantly improve PDT cytotoxicity against human cancer cells in vitro (Golding et al., 2013). This combination has proved effective in treatment of equine sarcoids (Golding et al., 2017). Other ways in which the efficacy of PDT may be improved

clinically include metronomic PDT, to deliver both the drug and light at very low dose rates over an extended period (hours to days) (Lilge et al., 2000), and the use of nanoparticles for PS delivery (Bechet et al., 2008). If the potential for use of PDT in veterinary medicine could be realised, this could make a significant contribution to the overall development of the technique.

Conclusions

PDT is a safe and effective therapy for many cancers and pre-cancers with external or endoscopic access. Long term clearance of small, localised lesions can be achieved, with negligible scarring or damage to adjacent structures. The science of PDT has seen enormous progress within the past 30 years, including the development of improved photosensitisers and light sources (including endoscopic delivery and daylight PDT), improved understanding of how PDT works, and expansion of the uses of photosensitisers to allow intraoperative detection of tumour margins. Although PDT has hitherto been used as a monotherapy, the future of the technique undoubtedly lies in combining it with other drugs and approaches as part of a synergistic multimodal treatment. Despite these scientific advances, the clinical practice of PDT is still limited to a small number of individual practitioners or centres of excellence, partly due to a vicious cycle of high photosensitiser costs due to limited demand. With pun intended, veterinary PDT needs to 'come out of the shadows and into the light'. This will only happen if PDT becomes a standard part of the training syllabus and if existing PDT practitioners provide training for the next generation of veterinarians. The referral system for PDT is also in need of improvement.

Conflict of interest statement

None of the authors of this paper have a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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